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REVIEW ARTICLE

dsRNA Virus Model Molecule and the Mechanism of PRRs and its Research Progress in Female Reproductive Tract Infections

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Abstract

Female animal genital tract opening on the body surface, prone to bacterial, viral, parasitic, and other pathogenic microorganism infections, leading to genital tract infectious diseases, such as endometritis, cervicitis, vaginitis, etc. Severe infection can lead to infertility, abortion, and even fetal death. Double-stranded RNA (dsRNA) is an important model molecule, which is widely present in the genome of viruses and generated in the process of virus replication. In mammals, dsRNA is considered to be an innate immune response signal for viral infection, which binds to the corresponding pattern-recognition receptors (PRRs) *In vivo* and then exerts biological functions. This review summarizes the signal transduction pathway induced by the binding of dsRNA model molecules to PRRs, research status of female genital tract infections and research progress of dsRNA in simulating viral infection in the female genital tract.

Key Words: *Genital tract infection; dsRNA; PRRs; Signal transduction*

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Introduction

Types of Viruses and Virus Model Molecules

Viruses are non-cellular microorganisms that can only parasitize in living cells of the host. Animals, plants, bacteria, and archaea are all the hosts of virus [1-4]. Virus can use the host's cellular system to replicate themselves, and they cannot survive independently. Viruses are generally composed of 2-3 structures: genetic material (RNA or DNA); a capsid formed by protein to wrap and protect the genetic material; some viruses can form a lipid envelope when they reach the host cell surface [5-7]. The genetic material of virus determines its virulence and host specificity. According to the genetic material of the virus, the nucleic acid type can be divided into DNA virus and RNA virus. The DNA virus has double-stranded while RNA virus has single-stranded. At present, more than 5000 types of viruses have been identified, and more of them are RNA viruses according to the identification.

Janeway referred to the main target molecules recognized by innate immune cells as pathogen-associated molecular patterns (PAMPs), and the corresponding recognition receptors as pattern recognition receptors (PRRs) [8]. Currently, PAMPs are generally defined as a class or a group of non-specific, highly conserved molecular structures shared by specific pathogens and their products that can cause inflammatory response in the host. These molecular structures are necessary for pathogens to survive and produce pathogenicity, and can be recognized by immune cells [9]. Studies have found that the nucleic acids of various types of viruses are recognized as PAMPs by host PRRs, like Toll-like receptors (TLRs) in the cytoplasmic endosomes, and induce signaling [10], such as viral CpG DNA activates TLR9; viral dsRNA activates TLR3; viral single-stranded RNA (ssRNA) activates TLR7/8. PAMPs that can be recognized by TLRs are not limited to nucleic acids. Many viral protein products can be recognized by TLR2 and TLR4. The virus protein products that have been confirmed as PAMPs include Measles virus hemagglutinin recognized by TLR2, F protein of respiratory syncytial virus (RSV) recognized by TLR4, and Env protein of mouse mammary tumor virus (MMTV). It is worth noting that viral dsRNA is a PAMP generated during the life cycle of most, if not all, viruses [11,12].

Molecular Structure and Biological Characteristics of dsRNA

Double-stranded RNA (dsRNA) adopts A-type helix structure, which is different from the typical DNA B-type helix structure. The main groove of dsRNA is narrower and deeper than DNA, while the sub groove of dsRNA is wider and shallower than DNA [13]. The unique phosphate backbone structure of dsRNA, and the unique 2'-OH exposed in the small groove, can be specifically recognized by protein kinase RNA-activated (PKR) and adenosine deaminase acting on RNA (ADAR), such as dsRNA Binding Domain (dsRBD) [14,15]. In particular, the narrow main slot of dsRNA contains sequence-specific information and is the site of interaction between protein and dsDNA [16]. The main slot does not allow the insertion of proteins, so proteins cannot interact with dsRNA bases. Correspondingly, the interaction between protein and dsRNA is mediated by small grooves and phosphate backbone, and does not depend on RNA sequence [14].

In addition to dsRNA viruses, dsRNA can also be derived from RNA replication intermediates during ssRNA virus infection or the symmetric translation process of DNA viruses [17,18].

Signal Transduction Pathway of dsRNA and Pattern-Recognition Receptors (PRRs)

Immunity is a state that protects the body from infection, including innate immunity and

acquired immunity. Innate immunity is the body's first line of defense against infection. Compared to acquired immunity, its specificity is poor, but it responds quickly. This efficient defense mechanism can inhibit the occurrence of most pathogen infections [19-21]. Pattern recognition receptors can be divided into two categories according to their subcellular locations: (1) TLR and C-type lectin receptor (CLR) on the cell membrane; (2) RIG-I-like receptors (RLR), absent in melanoma 2 (AIM2) and NOD-like receptors (NLR) in the cytoplasm [22-25].

In vertebrates, there are receptors that rely on viral RNA binding to activate their signal activity and effector functions [26,27]. These viral RNA-specific PRRs include TLR3/7/8, and retinoic acid-inducible gene I (RIG-I) and Melanoma Differentiation-Associated protein 5 (MDA5) in RLRs family [26]. Their effective antiviral immunity depends on the accurate recognition of viral RNA by the innate immune system. Except, TLR7 and TLR8 can recognize in viral ssRNA. These cell receptors and effectors can also recognize in dsRNA. Since the structure of dsRNA is considered to be a unique feature of viral RNA, it is generally believed that combining these dsRNA is sufficient to activate their respective antiviral functions [14]. In mammalian cells, TLRs, RLRs, and NLRs are important cytoplasmic nucleic acid sensors [28]. Among them, TLRs and RLRs are the two main receptors for the host to recognize viral PAMPs, and they are also the two most studied receptors [29-31].

TLR3-mediated antiviral response pathway

TLR3 is the only TLRs that can recognize virus-derived dsRNA and its synthetic analogue polyriboinosinic: polyribocytidylic acid (polyI:C) [32]. Interestingly, these nucleic acid sensitive TLRs are mainly located in the Intracellular compartment of nucleus, while other TLRs are located on the cell surface. TLR3 is mainly expressed in dendritic cells (DCs) and epithelial cells, such as respiratory tract, uterus, cornea and other epithelial cells [33].

The TLR3 pathway is a β-interferon TIR domain adaptor protein (TRIF)-dependent signaling pathway that does not require the participation of myeloid differentiation factor 88 (Myd88) [13]. The mechanism of TLR3 in antiviral and immunomodulatory response is shown in (Figure 1). After the receptor binds to dsRNA, the TLR3 signal is activated, leading to three main inflammation and innate immune pathways: (1) activation of interferon regulatory factor 3/7 (IRF3/7) and production of type I interferon (IFN-I) which mediate the development of antiviral responses; (2) activation pro-inflammatory transcription factors, nuclear factor κB (NF-κB) and activator protein 1 (AP-1) [34]; (3) induction of cytopathic effects or cell death in a caspase-8-dependent manner through receptors interacting protein 1 (RIP1) [35]. In addition, TLR3 signals can also regulate adaptive immune responses, such as enhancing the cytotoxic activity of T cells and mediating the cross-priming of cytotoxic T lymphocytes (CTLs) in CD8+DC cells [36]. The TLR3 signaling pathway can also up-regulate the expression of positive and negative costimulatory molecules on DCs, and affect the size of CD8+T cell responses [37].

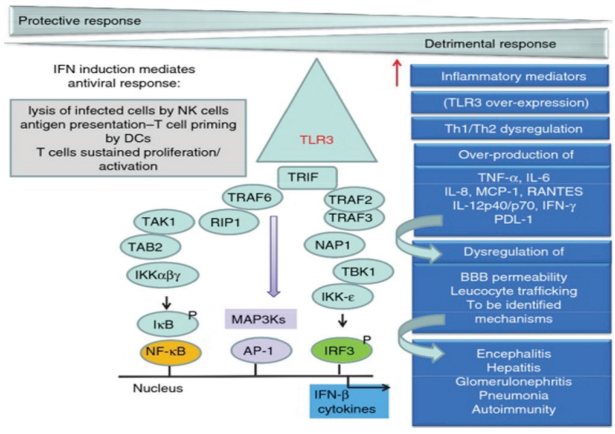

Figure 1) *Mechanism of action in antiviral and immunomodulatory response [35].*

RLRs-mediated antiviral response pathway

RLRs are a branch of the superfamily 2 (Superfamily 2, SF2) of helicases. It plays a role in recognizing dsRNA in cytoplasm. RLRs family molecules share a similar skeleton structure, bind to dsRNA in an ATP hydrolysis-dependent manner, and have double-stranded recognition specificity [38].

The three molecules in the RLRs family have certain differences in structure, so the dsRNA structures they recognize are different. RIG-I prefers to bind dsRNA fragments that are less than 1 kb, contain 5' triphosphate ends, and have complex secondary structures [39]. The 5' triphosphate terminal alone cannot fully activate RIG-I, and at least part of the dsRNA in the 5' terminus is required to fully activate RIG-I. MDA5 was initially reported to bind dsRNA larger than 1kb, but subsequent studies suggested that MDA5 is activated by the RNA network structure, which is formed by the extension of branched RNA [40]. Moreover, the binding of MDA5 to dsRNA is not necessarily related to the end of dsRNA, because the C-terminal domain (CTD) of MDA5 is different from the CTD of RIG-I. The CTD of the MDA5 has a flat surface structure and does not have the pocket structure of RIG-I. Therefore, MDA5 does not bind to the end of dsRNA or the 5' triphosphate structure, but binds to the skeletal structure parallel to the helix of dsRNA [40]. The dsRNA recognition mechanism of LGP2 is still unclear, and the regulatory role of LGP2 in the production of IFN-I remains controversial. Some studies suggested that it can negatively regulate the production of IFN-I, while other studies suggested that it can positively regulate the production of IFN-I. In addition, the structure of the proposed LGP2 RNA-binding domain is different from that of RIG-I and MDA5. LGP2 can recognize not only dsRNA and 5' triphosphate terminal structural RNA, but also part of ssRNA [41]. The ability of RLRs to recognize different types of RNA ligands reflects their ability to recognize various viruses.

LGP2 itself does not have immune signal activity, but it is thought to up-regulate and down-regulate the signal activity of MDA5 and RIG-I, respectively [42].The mechanism of RIG-I/MDA5 contributing to antiviral response is shown in (Figure 2). The activation of RIG-I/MDA5 can lead to the formation of a signaling complex, which consists of mitochondrial antiviral signaling protein (MAVS) (also known as IPS-1, CARDIF or VISA), tumor necrosis factor receptor related Protein (tumor necrosis factor (TNF) receptor-associated factors, TRAFs), TRAF family-related NF-κB activator protein-binding kinase 1, and NF-κB inhibits protein kinase ε (inhibitor of nuclear factor κ B kinase ε, IKKε). Then, NF-κB, IFN regulatory factors 3 (IFN regulatory factors 3, IRF3)/IRF7, and activating transcription factor (ATF)/immediate early gene (c-Jun) will be phosphorylated, activated, and moved into the nucleus to induce the expression of pro-inflammatory factors, such as necrosis factor α (TNF-α) and interleukin-6 (IL-6), and IFN-I [43, 44]. Subsequently, the IFN-I induced by RIG-I binds to its receptors on the same cells or surrounding cells, generating a cascade of amplification effect and inducing the expression of a large number of anti-virus-related interferon-stimulating genes (ISGs) [45]. Some of ISGs can directly interfere with the replication of the virus, such as ribonuclease L (RNase L), 2'-5' oligoadenylate synthase (OAS), PKR, and interferon-induced endoplasmic reticulum associated virus inhibitory protein (Viperin); some of ISGs are PRRs or interferon regulatory factors (IRF), which can further promote the expression of IFN-β and ISGs [46]. These ISGs synergistically exert an anti-viral effect to help the host cell clear the infected virus.

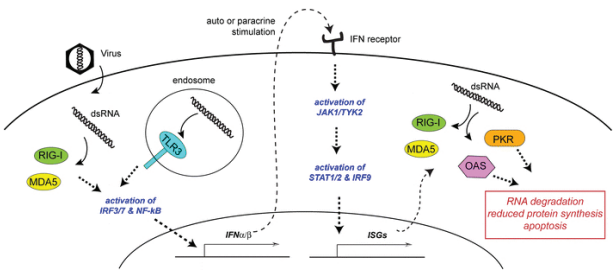

Figure 2) *The mechanism of action of RIG-I/MDA5 in the antiviral response [14].*

Status of Female Reproductive Tract Virus Infection

CLRs is an important type of PRRs, which can recognize a wide range of pathogens on the surface of dendritic cells (DCs) [47-48]. CLRs exists in female genital tract and is mainly expressed in epithelial cells [49,50]. DC precursor cells express different CLRs under different stimuli, which plays a critical role in HIV-1 infection and spread in the female reproductive tract *In vivo* [51]. Therefore, the types and levels of CLR expressed by DCs can be used to be evaluate the impact of mucosal delivery vectors on HIV-1 infection and spread, providing an *In vitro* research tool for evaluating the safety evaluation of mucosal vaccines, adjuvants, and drugs.

Studies have shown that symbiotic bacteria unique to the female reproductive tract can stimulate the DC precursor cell line THP-1 to express Cdla, CD324, CCR6 and the other surface markers related to Langerhans cells (LC). Langerin/CD207 is a more specific CLR that is unique to LC, which can bind to HIV-1 with high affinity, thereby capturing and inactivating the virus and preventing its infection and spread. More studies have found that *L.crispatus* can stimulate THP-1 cells to express Langerin/CD207 at a high level, accompanied by a significant upregulation of phagocytic ability and the expression of Th1 cytokines, suggesting that *L.crispatus* can induce functional LC, which can prevent HIV-1 virus infection and spread in the body. Therefore, the peculiar symbiotic bacteria of the female genital tract can be used as mucosal immune vaccine delivery vector strains for further in-depth research.

Research Status of dsRNA in Female Reproductive Tract Mimic Virus Infection

With the prevalence of human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome, it is urgent to find corresponding solutions. Secreted leukocyte protease inhibitor (SLPI) and Trappin-2/Elafin belong to the whey acidic protein (WAP) family, produced by a variety of cells, secreted in mucosal secretions, and increased by inflammation [52]. Trappin-2/Elafin is a serine protease inhibitor, which acts as an important anti-inflammatory mediator on the mucosal surface. Trappin-2/Elafin has been found to be involved in skin immune disorders, such as psoriasis 42 and chronic obstructive pulmonary disease (COPD 43) [53,54]. SLPI interacts with cell membrane proteins and can disrupt virus entry and fusion. SLPI has been proven to be an important inhibitor of HIV, but there is no report of Trappin-2/Elafin as an anti-HIV molecule [55]. Although the mechanism by which Trappin-2/Elafin inhibits HIV-1 has yet to be determined, its homology with SLPI indicates that its mechanism of action may be similar to SLPI.

Detect Trappin-2/Elafin produced by epithelial cells of the female upper and lower reproductive tract, and its activity as an anti-HIV-1 molecule. It was found that the primary uterus, fallopian tubes, cervix, and outer cervical epithelial cells constitutively produced Trappin-2/Elafin. Stimulation using the human synthetic viral dsRNA mimics poly(I:C) [56] increases the secretion of Trappin-2/Elafin increases, especially in uterine cells. Recombinant Trappin-2/Elafin inhibiters T cell X4/IIIB and macrophage R5/BaL HIV-1 in a dose-dependent manner [57]. However, using the cervicovaginal lavage, it was found that the average level of Trappin-2/Elafin secreted by HIV-negative women appear to be higher than that by HIV-positive women, even though there was no statistical significance. Trappin-2/Elafin has been suggested to be an important endogenous antiviral molecule in the female reproductive tract for HIV-1 [57].

Infectious pathogens can pass through the

maternal blood or the urinary system to the uterus to reach the placenta, and then colonize the maternal decidua. Decidual stromal cells (DSCs) are the main cell type in the decidua. DSCs express molecules of the innate immune system and various sensors that can identify PAMPs. During pregnancy, viral infections can lead to miscarriage and premature delivery. Both decidual and endometrial stromal cells are sensitive to common intrauterine viruses (including Human Cytomegalovirus and Zika virus) [58,59], leading to adverse pregnancy.

Poly(I:C) has been used to study the effect of viral dsRNA on DSCs in early pregnancy. Transfection of poly(I:C) induces DSCs necroptosis in a RLRs/IPS-1 dependent manner, while extracellular dsRNA induces DSCs necroptosis in a TLR3/TRIF-dependent manner. Poly(I:C) induces reduced stromal cell death and milder pathological changes in the uterus of mixed-lineage kinase domain-like protein (MLKL) mice [60]. This suggest that intervention in the signaling pathways leading to necrosis of DSCs potentially help prevent and treat abnormal pregnancy induced by viral dsRNA. These findings also suggest a relationship between DSCs necrosis and pregnancy-related diseases, and thus potentially provides a new treatment strategy to reduce the adverse effects of viral infections during pregnancy.

Summary and Prospect

The female reproductive tract can respond immediately to viral infection through TLR3 and RIG-I/MDA5 in the local innate immune system and produce inflammatory mediators and the related regulatory factors. The balance of this local innate immune response is essential for eliminating pathogens and viral infected cells. Meanwhile, strong inflammatory responses may lead to tissue damage and autoimmune diseases such as endometritis. Therefore, understanding the regulatory mechanism of the PPRs-mediated innate immune responses against viral infection in the female reproductive tract can help develop the preventatives and therapies for the viral infection and related disease in the female reproductive tract.

In addition, dsRNA is involved in post-transcriptional gene silencing in eukaryotic organisms, which regulates gene expression and causes changes in non-coding RNA. Non-coding RNAs play key roles in various physiological processes, including cell proliferation, development, differentiation, and apoptosis, as well as disease manifestations, tumorigenesis, and viral infections. However, in the current research on dsRNA-induced antiviral response in the female reproductive tract and the regulatory function of non-coding RNAs remain unclear. This passage provides a theoretical basis for understanding how non-coding RNA participates in regulating the antiviral response of female animals' reproductive tract.

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